UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/933,131	08/21/2001	Li Zhang	10723-26	4949

7590 08/26/2003

MICHELINE & GRAVELLE
Bereskin & Parr
Box 401
40 King Street West
Toronto, ON M5H 3Y2
CANADA

EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	11

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,131	ZHANG ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 06/19/03 (Paper No. 10), is acknowledged.

Claims 1-11 are pending.

Claims 2-3 and 8-11 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1 and 4-7 are under consideration in the instant application.

In view of the amendment, filed 06/19/03 (Paper No. 10), the following rejection remains

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to inhibit lymphoma cell growth and a method to treat lymphoma, comprising administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$ does not reasonably provide **enablement** for a method to inhibit any tumor cell growth and a method to treat or prevent any cancer comprising administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action, Paper No: 8, mailed 02/11/03.

Applicant's arguments, filed 06/19/03 (Paper No. 10), have been fully considered, but have not been found convincing.

Applicant asserts that one of skilled in the art would readily expect that the regulatory T cells of the invention would be able to kill all types of tumors based on their ability to kill the aggressive lymphoma cells used in the application.

Contrary to Applicant's assertion, the issue raised in the previous Office Action, was that the specification only discloses that administering effective amount of regulatory T-cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$ can inhibit growth of lymphoma cells in Scid (severe combined immunodeficient) mouse as a test animal (Example 1 of the Specification as filed).

The specification does not adequately teach how to effectively inhibit any tumor cell growth or proliferation such as treating any cancer or reach any therapeutic endpoint in mammals by administrating effective amount of regulatory T-cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-$ $CD8^-CD44^-$ Cd28-$NK1.1^-$. It is not clear that reliance on the *in vivo* data of treating lymphomas , that was induced in immunodeficient mice in response to A20 B cell leukemia/lymphoma cells inoculation into said mice, after administrating effective amount of regulatory T-cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-NK1.1 accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from limited *in vivo* assay studies to the development of effective *in vivo* mammalian therapeutic treatment, commensurate in scope with the claimed invention.

Moreover, an effective protocol for inhibiting tumor growth in a human patient is a subject to a number of factors which enter the picture beyond simply the administration of an effective amount of a regulatory T cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-NK1.1. Demonstration that administering effective amount of regulatory T-cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$ can prevent growth of lymphoma cells in Scid mouse, that was induced in said mouse in response to A20 B cell leukemia/lymphoma cells inoculation cannot alone support the predictability of the method of treating *any* tumor growth. The establishment and growth of a tumor is a subject to variables. The ability of a host to suppress and thereby prevent the tumor from establishing itself will vary depending upon factors such as the condition of the host, the type of tumor (rapidly proliferating or slowly proliferatinf) and the tumor burden.

Chatterjee et al. (Cancer Immunol. Imunother., 1994, v.38, pages 75-82 see Introduction) state the art recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap. Results obtained under controlled conditions and in inbred animals, as in the instant specification where Scid (severe combined immunodeficient) mice are used as a test animal, often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy. For example, Dermer

(Biotechnology 12: 320, 1994) states that the widely disparate character of human tumor cells contributes greatly to chemotherapy's continued ineffectiveness against cancer. Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. **Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.**

In addition, Sussman et al.(Annals of Surgical Incology, 1994, v.1 p296-306) teach that hampering the development of the effective immunotherapy of human cancer is the poorly defined immunosuppression that occurs in cancer patient, due to the presence of tumor suppressor cells in tumor-bearing host that abrogate the antitumor reactivity of adoptively transferred immune lymphocytes. Sussman et al further teach that there is significantly less information regarding the phenomenon of tumor-induced suppression that may inhibit the development of immune cells. (see entire document, page 303 in particular).

Simillary, Klingemann (J. of Hematotheraphy and Stem Cell Research, 2001, v.10, p 23 –26) teaches that cellular adoptive immunotherapy should never bee expected to be useful and **effective against all tumor burden**. Such therapy should be viewed as a part of a comprehensive cancer treatment approach that may include chemotherapy, radiation and other novel treatment. Expecting anything more would be unrealistic and may call a negative outcome of studies if they are designed with such an end point in mind (see entire document, page 25 in particular).

The specification does not provide sufficient teaching as to how it can be assessed that treatment of any tumors or any cancer was achieved after administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ $\alpha\beta$ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method to inhibit any tumor cell growth or proliferation and method to treat any cancer comprising administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ $\alpha\beta$ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$ in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

3. No claim is allowed.

4. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
August 21, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600